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N-Acetyltransferase Polymorphisms and Colorectal Cancer: A HuGE Review

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The two expressed genes coding for *N*-acetyltransferase (NAT) activity, *NAT1* and *NAT2*, are located on chromosome 8 at 8p21.3–23.1 and are polymorphic. Both enzymes are capable of *N*-acetylation, *O*-acetylation, and *N,O*-acetylation and are implicated in the activation and detoxification of known carcinogens. Single base-pair substitutions in *NAT2* tend to occur in combination with other substitutions within the gene. As yet, less work has been done to characterize *NAT1* allelic variants. Various methods for the detection of the reported polymorphisms exist. It is important to select a method that is appropriate to the population being studied. The functional significance of many NAT allelic variants has not been determined. Geographic and ethnic variation in the frequency of *NAT2* genotypes associated with fast or intermediate acetylation has been observed. Insufficient data for *NAT1* genotypes are available to reveal a clear geographic pattern. No consistent association has been found between acetylator phenotype or genotype and colorectal cancer. The lack of consistency can in part be accounted for by methodological factors, including limited statistical power. Possible interactions between the NAT genes and either environmental exposures or other polymorphic genes encoding xenobiotic metabolizing enzymes have been investigated in only a minority of these studies, and these studies have lacked statistical power to detect interactions. *Am J Epidemiol* 2000;151:846–61.

colorectal neoplasms; epidemiology; genetics; *N*-acetyltransferase; *NAT1*; *NAT2*

GENE

In humans, there are three *N*-acetyltransferase (NAT) loci: two expressed genes, *NAT1* and *NAT2*, and a pseudogene, *NATP*. Both expressed genes are 870 base-pair intron-less protein coding regions encoding 290 amino acid proteins (1) and are located on chromosome 8 (2) at 8p21.3–23.1 (3).

The two isozymes use acetyl coenzyme A as a cofactor and function as phase II conjugating enzymes (4); they are capable of *N*-acetylation, *O*-acetylation, and *N,O*-acetylation (5). *N*-acetylation is a detoxification pathway. *O*-acetylation and *N,O*-acetylation occur in alternative metabolic pathways following activation by *N*-hydroxylation. The isozymes differ in their substrate specificities: Isoniazid and sulfamethazine are NAT2-specific substrates; *p*-aminobenzoic acid and *p*-aminosalicylic acid are NAT1-specific substrates. Among the enzyme substrates are several carcinogenic compounds, many of which are present in cooked food and tobacco smoke (6). This has prompted speculation that the NAT enzymes and the genes encoding them may be involved in susceptibility to cancer, including colorectal cancer, because of the presence of carcinogenic heterocyclic amines in some cooked foods (7).

NAT2 is primarily expressed in the liver, whereas NAT1 is primarily expressed at other sites, including the colon (8). In colon tissue removed from cadavers, the ratio of NAT1 activity to NAT2 activity was found to change along the length of the intestine (9). Differences between the relative levels of isozyme activity were most marked in the distal colon; in one individual, 50- to 70-fold higher NAT1 activity than NAT2 activity was observed.

GENE VARIANTS

The polymorphic nature of human NAT was first described in 1953 (10); a proportion of individuals receiving isoniazid therapy suffered adverse neurologic side effects due to an accumulation of unmetabolized drug. Family pedigree studies confirmed the genetic basis of the variation (11). Specific single base-pair substitutions responsible for altered enzyme activity were first reported in 1990 (2).

NAT2 allele classification and nomenclature

Three NAT2 phenotypes have been described. The fast acetylation phenotype results from possession of

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Abbreviations: CI, confidence interval; CYP1A1, cytochrome P4501A1; CYP1A2, cytochrome P4501A2; GSTM1, glutathione *S*-transferase class M1; GSTT1, glutathione *S*-transferase class T1; NAT, *N*-acetyltransferase; NAT1, *N*-acetyltransferase type 1; NAT2, *N*-acetyltransferase type 2; RR, relative risk.

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two copies of the wild-type allele. If only one allele is wild-type, an intermediate phenotype is observed. Persons with the slow acetylator phenotype possess two mutated alleles. Many early studies did not distinguish between fast and intermediate acetylators, categorizing both types of subjects as fast acetylators.

The first *NAT2* alleles described were termed M1, M2, and M3. M1 consisted of a transition at nucleotide 481 ($C^{481}T$) together with $T^{341}C$; M2 consisted of a transition of $C^{282}T$ and $G^{590}A$; and M3 consisted of a transition of $G^{857}A$. Alleles M1 and M2 accounted for 90 percent of the slow acetylators in the original study (12), which included 18 subjects phenotyped in vivo and 26 liver samples phenotyped in vitro. M3 was first described in Japan (13).

The identification and characterization of new allelic variants by many different laboratories gave rise to conflicting allele designations, which complicated the interpretation of earlier studies. The scheme suggested by Vatsis et al. (5) (table 1) provides a nomenclature of currently recognized NAT alleles and facilitates the inclusion of any further alleles. The use of this scheme has simplified the interpretation of more recent studies. According to this nomenclature (5), M1, M2, and M3 should now be termed *NAT2**5A, *NAT2**6A, and *NAT2**7A, respectively.

Ten point mutations have been reported in *NAT2* (5), each a single base-pair substitution. Many published reports have investigated only single mutations and have based allele designations on this. However, recent improvements in techniques for detecting individual polymorphic sites have shown that isolated single substitutions are uncommon; combinations of mutations are more common. Within certain populations, some substitutions have been consistently observed to cosegregate (e.g., $C^{481}T$ rarely occurs without $T^{341}C$ (14)).

Functional significance of *NAT2* mutations

The *NAT2* alleles described so far may contain up to four of the 10 reported mutations (5). The functional significance of most combinations is unknown. However, it is plausible that each combination might result in a different phenotype.

The functional significance of the 10 mutations is summarized in table 2 (12, 13, 15–19). Some of the mutations change the amino acid sequence of the resultant enzyme, but not all of these have been observed to alter phenotype (e.g., $A^{803}G$ (19)). However, some mutations have been consistently observed to reduce acetylation activity (e.g., $T^{341}C$)

TABLE 1. Human *N*-acetyltransferase type 2 (*NAT2*) allele designations*

Allele	Substitution†									
	$C^{481}T$	$C^{282}T$	$C^{759}T$	$G^{191}A$	$T^{341}C$	$A^{434}C$	$G^{590}A$	$A^{803}G$	$G^{845}C$	$G^{857}A$
*NAT2*4* (wild-type)										
*NAT2*5A*	X				X					
*NAT2*5B*	X				X			X		
*NAT2*5C*					X			X		
*NAT2*5D*					X					
*NAT2*5E*					X		X			
*NAT2*5F*	X		X		X			X		
*NAT2*6A*		X					X			
*NAT2*6B*							X			
*NAT2*6C*		X					X	X		
*NAT2*7A*										X
*NAT2*7B*		X								X
*NAT2*12A*								X		
*NAT2*12B*		X						X		
*NAT2*12C*	X							X		
*NAT2*13*		X								
*NAT2*14A*				X						
*NAT2*14B*		X		X						
*NAT2*14C*	X			X	X			X		
*NAT2*14D*		X		X			X			
*NAT2*14E*				X				X		
*NAT2*14F*		X		X				X		
*NAT2*17*	X				X	X		X		
*NAT2*18*									X	

* Source: Vatsis et al. (5) (updated by personal communication, 1998).
† C, cytosine; T, thymine; G, guanine; A, adenine.

TABLE 2. Functional significance of *N*-acetyltransferase type 2 (*NAT2*) mutations

Substitution*	Amino acid sequence change*	Observed in combination with one or more of:	Correlation with phenotype†	Article
$C^{481}T$	Silent	$T^{341}C$, $A^{803}G$, $C^{759}T$, $G^{191}A$, $A^{434}C$	No change alone but necessary for $T^{341}C$ to affect activity	Blum et al., 1991 (12)
$C^{282}T$	Silent	$G^{590}A$, $A^{803}G$, $G^{857}A$, $C^{282}T$, $G^{191}A$	No change	Blum et al., 1991 (12)
$C^{759}T$	Silent	$C^{481}T$, $T^{341}C$, $A^{803}G$	No change	Woolhouse et al., 1997 (15)
$G^{191}A$	$Arg^{64}Gln$	$C^{282}T$, $C^{481}T$, $T^{341}C$, $A^{803}G$, $G^{590}A$	Reduced enzyme activity, highly conserved region of the active site for acetyl transfer	Bell et al., 1993 (16); Deloménie et al., 1996 (17)
$T^{341}C$	$Ile^{114}Thr$	$C^{481}T$, $A^{803}G$, $G^{590}A$, $C^{759}T$, $G^{191}A$, $A^{434}C$	Reduces enzyme activity if combined with $C^{481}T$	Blum et al., 1991 (12)
$A^{434}C$	$Gln^{145}Pro$	$T^{341}C$, $C^{481}T$, $A^{803}G$	Unknown	Lin et al., 1994 (18)
$G^{590}A$	$Arg^{197}Gln$	$C^{282}T$, $T^{341}C$, $A^{803}G$, $G^{191}A$	Reduces half-life of protein (from 22 hours to 6 hours); affinity unchanged	Blum et al., 1991 (12)
$A^{803}G$	$Lys^{268}Arg$	$G^{191}A$, $C^{282}T$, $T^{341}C$, $C^{481}T$, $C^{759}T$, $A^{434}C$	No change if alone	Cascorbi et al., 1996 (19)
$G^{845}C$	$Lys^{282}Thr$	None	Unknown	Lin et al., 1994 (18)
$G^{857}A$	$Gly^{286}Arg$	$C^{282}T$	Decreased activity	Ohsako and Deguchi, 1990 (13)

* C, cytosine; T, thymine; G, guanine; A, adenine; Arg, arginine; Gln, glutamine; Ile, isoleucine; Thr, threonine; Pro, proline; Lys, lysine; Gly, glycine.

† Information given in this column suggests the likely effect of the given mutation if present alone. However, this effect may be modified by the presence of other mutations.

(20). The functional effect on phenotype is due to impairment of the protein translation or stability; messenger RNA levels are not altered (12). For several of the mutations, their designation as "fast" or "slow" is not yet definitive.

The $C^{481}T$ transition does not change the amino acid sequence; however, it has always been found with other mutations. In populations of European origin, $C^{481}T$ most often occurs with $T^{341}C$ and $A^{803}G$; when $C^{481}T$ is combined with $T^{341}C$, enzyme activity is reduced. $G^{191}A$ was discovered because of phenotype/genotype discordance in African-American subjects (16). Site-directed mutagenesis (serial replacement of nucleotides within the gene coding region) showed codon 64 to be highly conserved between species, and it is implicated as the active site for acetyl transfer (17). Disruption of this region has been demonstrated to abolish enzyme activity in vitro.

In European populations, relatively high concordance between acetylator phenotype (for *NAT2*-specific substrates) and *NAT2* gene mutations has been demonstrated (12, 21).

NAT1 allele nomenclature

Until the study by Weber et al. (22) revealed several allelic variants, *NAT1* was assumed to be monomorphic. The original alleles, designated V_1 (wild-type), V_2 ($T^{1088}A$ and $C^{1095}A$), and V_3 ($C^{-344}T$, $A^{-40}T$, a nine-base-pair deletion between nucleotides 1065 and 1090, and $C^{1095}A$), have now been incorporated into the Vatsis nomenclature (5) and redesignated *NAT1**4, *NAT1**10, and *NAT1**11, respectively.

Functional significance of *NAT1* alleles

Interindividual variation in NAT1 activity has been reported. In addition, a twofold intraindividual variation in activity (in 75 peripheral blood samples) was observed over a 10-week period (23). If this finding is confirmed, it might suggest that NAT1 is inducible by exposure to endogenous or exogenous factors.

The functional significance of the *NAT1* allelic variants has not been fully established. Mutations can both increase and decrease the acetylation capacity relative to the wild-type allele. On the basis of the studies published to date (24–26), *NAT1**4 is considered the wild type. The alleles that are believed to increase *NAT1* acetylation capacity are *NAT1**10, *21, *24, and *25. Alleles *NAT1**14, *15, *17, *19, and *22 give rise to enzymes with reduced activity or no detectable activity. Alleles *NAT1**11, *20, and *23 produce enzymes with acetylation capacity similar to that of *NAT1**4. The current allele designations refer mainly to single substitutions, insertions, or deletions. It is possible that combinations of these substitutions will be found to occur; these combinations may have functional consequences.

Population frequencies

We searched MEDLINE® and EMBASE using the Medical Subject Heading "arylamine *N*-acetyltransferase" and the text words "NAT," "*NAT1*," "*NAT2*," and "*N*-acetyltransferase." We also used the Medical Literature Search procedure in the Office of Genetics and Disease Prevention at the Centers for Disease Control and Prevention (Atlanta, Georgia). In addition, we reviewed reference lists in published articles. We identified and critically appraised relevant articles. This section includes studies reporting phenotype and genotype frequencies in a variety of individuals without cancer (7, 14, 16, 18, 21, 23, 27–95). (Complete data are presented in a table on the Human Genome Epidemiology Network website (http://www.cdc.gov/genetics/hugenet/default.htm).) Because phenotype cannot be imputed, we excluded studies reporting only the frequency of individual mutations or alleles.

In many published articles, the study's subject selection criteria were not stated. When they were stated, the criteria were diverse. Some studies included disease-free subjects matched to diseased patients on characteristics such as age and sex; others were based on hospitalized subjects, specific occupational groups, or volunteers for whom the recruitment procedure was not described. This made it difficult to determine the extent to which apparent geographic or ethnic variation reflected biologic differences or methodological factors. For example, the lowest frequency of fast/intermediate *NAT2* acetylation genotypes reported in Europe (12 percent) was based on specimens obtained from a cell bank in France (52); this frequency was substantially lower than the frequencies of 39 percent and 47 percent observed in other studies carried out in France (53, 54) and elsewhere in Europe.

In most *NAT2* genotype studies, only a limited number of "indicator" mutations, thought to be tightly linked with other mutations and predictive of acetylator status, have been investigated. This is likely to have led to underestimation of the proportion of *NAT2* slow acetylators. The designation of alleles according to the presence/absence of "indicator" mutations assumes particular patterns of linkage, which may not be tenable in other populations or ethnic groups. For example, the genotype-phenotype discordance observed for African Americans and US Hispanics may result from compound alleles that are different from those observed in other populations (14).

The frequency of *NAT2* genotypes associated with fast or intermediate acetylation varies markedly between, and to some extent within, continents. The highest frequency occurs in Asia, particularly in Japan (approximately 90 percent). The frequencies reported in other Southeast Asian populations are: 73 percent in Hong Kong (14), 72 percent in Malaysia (46), and 58 percent in Singapore (47). Studies carried out in other parts of Asia have reported lower frequencies: 32 percent in India (39), 37 percent in the United Arab Emirates (49), and 43 percent in Turkey (48). In most European populations, approximately 40 percent of study subjects have genotypes associated with fast or intermediate acetylation. Genotype frequencies within the United States vary by ethnic group: for White subjects, frequencies are similar to those of European populations, and for Asians, they are similar to those of populations in Southeast Asia. The lowest frequencies have been reported in two small African studies in which subject selection was not described (27). Interestingly, higher frequencies have been reported in African Americans (14).

All but three of the studies (83, 84, 88) of the NAT phenotype used *NAT2* substrates. The geographic variation in the frequency of the fast/intermediate NAT phenotype is generally consistent with that observed for the *NAT2* genotype.

Few studies to date have investigated the *NAT1* genotype. So far, *NAT1**10 is the most common variant of those investigated. The reported frequency of wild-type homozygosity ranges from 24 percent to 96 percent. In the United Kingdom alone, variation of 29–96 percent was observed. The frequency of *NAT1* wild-type homozygosity within a study depends on the alleles investigated. Hubbard et al. (95) considered *NAT1**14 and *NAT1**15, whereas Bell et al. (25) examined *NAT1**3, *NAT1**10, and *NAT1**11. In the United States, the wild-type homozygote frequencies are 44–62 percent among Whites (35, 38) and, in the one study with published results, 24 percent among African Americans (35). Studies carried out in Australia (23) and Japan (42) reported frequencies of 92 percent and 38 percent, respectively.

DISEASE

Worldwide in 1996, an estimated 876,000 new cases of colorectal cancer occurred—445,000 in males and 431,000 in females (96). Less than one third of colorectal cancer cases occur in developing countries (97). In developed countries, colorectal cancer is the second most common cancer in both sexes (97).

World age-standardized incidence rates are lowest—approximately 10 per 100,000 population per year—in Africa, India, and Thailand and in some Chinese populations (98). The highest rates—more than 40 per 100,000 in men and more than 30 per 100,000 in women—are observed in North America, Northern Europe, Australia, and New Zealand. In many populations, colorectal cancer incidence rates have been rising (99), with the greatest increases being observed in Japan. For example, in Miyagi, Japan, the rate among males increased from 19.7 per 100,000 in 1978–1981 to 41.5 in 1988–1992, and the rate among females increased from 16.8 per 100,000 to 24.8 per 100,000 (98, 100).

Less than 10 percent of colorectal cancers are believed to be due to recognized genetic syndromes (familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer) (101). After exclusion of these syndromes, however, familial aggregation has been observed (102, 103), which suggests that genetic susceptibility may play a role in disease etiology. Results of migrant studies indicate that environmental factors have an important influence (104, 105). Thus, this evidence suggests that the majority of cases are probably due to a combination of environmental or lifestyle exposures and genetic susceptibility.

A high intake of vegetables is inversely associated with the risk of colorectal cancer, and it is possible that increased intakes of fiber, starch, and carotenoids are protective (106). There is consistent evidence that the most physically active groups in the population are at lower risk (107). On the basis of evidence from over 20 observational studies, it has been concluded that regular use of aspirin reduces risk (108).

Increased risk has been associated with diets high in sugar, total and saturated fat, eggs, and processed meat, although the evidence is inconsistent (106). More consistent evidence exists for a positive association with red meat consumption (106), with increased risk possibly being due to exposure to the heterocyclic aromatic amines formed when meat is cooked to pyrolytic temperatures (6) rather than to consumption of meat per se (109). A recent large case-control study found that although "usual" dietary intake of heterocyclic amines was not associated with increased colon or rectal cancer risk, very high daily intake was (110). A role for the NAT enzymes in the activation of heterocyclic aromatic amines has been proposed (109). The NAT enzymes are also involved in the activation of aromatic amines (7) found in tobacco smoke (111). While tobacco smoking has consistently been associated with adenomatous polyps, the evidence with regard to colorectal cancer is less strong (112). While some recent large cohort studies have suggested that smoking may increase risk after a long latency period (113–116), this has not been a consistent finding (117).

ASSOCIATIONS

The studies discussed in this section and the following section were identified using the search strategy described above, with the addition of Medical Subject Headings and text words relevant to colorectal cancer or polyps. The studies are summarized in tables 3 and 4 (7, 8, 24, 25, 30, 31, 37, 38, 40, 66, 78, 81, 90, 95, 118–126).

Until genotyping techniques were developed (2), investigations of the relation between acetylator status and colorectal cancer relied on phenotyping. Probe drugs such as isoniazid, sulfamethazine, and caffeine were administered and the metabolites were measured by high performance liquid chromatography. If the probe drug was NAT2-specific (as it is for most studies), it would fail to account for NAT1 activity. NAT1 phenotyping has been done to validate genotyping or to investigate the effects of individual alleles, but it has not been used in assessing the association between colorectal cancer and acetylator status. In case-control studies, phenotypic assessment of acetylation may be influenced by disease status.

Five studies have investigated the association between acetylator phenotype and colorectal cancer (table 3) (7, 90, 119–121); two of them simultaneously investigated phenotype and colorectal adenomatous polyps (120, 121). Four of the five cancer studies (7, 90, 119, 120) and one of the polyp studies (120) used NAT2-specific probe drugs. Table 4 summarizes data from 11 studies of the relation of *NAT2* genotype to colorectal cancer (8, 25, 37, 38, 40, 66, 78, 81, 122, 123, 125, 126) and three studies of polyps (24, 30, 31, 124). The participants investigated by Lin et al. (24) overlap with those investigated by Probst-Hensch et al. (30, 124). Five cancer studies (25, 38, 95, 123, 125) and two polyp studies (24, 30) also investigated *NAT1* genotype (table 4).

Colorectal neoplasia and acetylator phenotype

The results of three of the four studies using NAT2-specific probe drugs suggested a positive association between the fast acetylator phenotype and colorectal cancer (7, 119, 120). In the fourth study, no association with colorectal cancer was found (90). Roberts-Thompson et al. (120) also analyzed a series of polyps; no association was found with acetylator phenotype. Lang et al. (121) used caffeine, which is not an NAT2-specific substrate, to determine acetylator status; no association with cancer and polyps was found (relative risk (RR) = 1.3; 95 percent confidence interval (CI): 0.8, 2.3).

Colorectal cancer and *NAT2* genotype

In 10 of the 11 studies of invasive colorectal cancer and *NAT2* acetylator genotype (table 4), no association with fast/intermediate acetylator genotype was observed. The remaining study reported a statistically

TABLE 3. Summary of studies of colorectal neoplasia and acetylator phenotype

Phenotype and area of study	Cases		Controls		Relative risk for fast and intermediate acetylators vs. slow acetylators		Exposure assessment	Article
	Type	No.	Type	No.	RR*	95% CI*		
NAT2*-specific phenotype								
Australia, West	Patients who had undergone surgical resection for colorectal adenocarcinoma; 71% male	49	Patients and volunteers of similar age, sex, and ethnicity as cases; without cancer; 80% male	41	3.8	1.5, 9.3	Smoking and alcohol assessed; not analyzed with acetylator status	Ilett et al., 1987 (119)
Australia, South	Cases with colorectal cancer from one hospital; 55% enrolled prospectively, 45% with resection within the preceding 2 years; Whites, median age of 69 years	110	Subjects who had undergone colonoscopy or barium enema in the same hospital as cases who had no neoplastic lesions; Whites, median age of 69 years	110	1.8	1.0, 3.3	Meat consumption assessed; analyzed with phenotype	Roberts-Thomson et al., 1996 (120)
	Subjects who had undergone colonoscopy or barium enema in same hospital as cancer cases who had histologically confirmed colorectal adenomas; Whites, median age of 69 years, male: female ratio 2:1	89	Same control group as above		1.1	0.6, 2.1		
Spain	Cases of histologically diagnosed colorectal cancer; 48% male	109	"Healthy" subjects; source not stated; 44% male	96	1.1	0.7, 2.0	None	Ladero et al., 1991 (90)
United States, Arkansas	Male hospital patients with a history of colorectal cancer	43	Male hospital patients without malignant disease	41	2.5	1.0, 6.4	Diet, smoking, exercise, medical history, and occupational history assessed; analyzed with phenotype	Lang et al., 1986 (7); Wohleb et al., 1990 (118)
Nonspecific acetylator phenotype								
United States, Arkansas	Subjects with colon cancer (n = 34) or colon polyps (n = 41) admitted to one hospital; 56% male; mean age = 60 years	75	Subjects selected by random digit dialing in central Arkansas; 63% male; mean age = 47 years	205	1.3	0.8, 2.3	Diet, meat cooking preference, and smoking status assessed; analyzed with NAT2 and CYP1A2* phenotypes combined	Lang et al., 1994 (121)

* NAT2, *N*-acetyltransferase type 2; RR, relative risk; CI, confidence interval; CYP1A2, cytochrome P4501A2.

TABLE 4. Summary of studies of colorectal neoplasia and the *N*-acetyltransferase type 1 (*NAT1*) and type 2 (*NAT2*) genotypes

Area of study	Cases		Controls		*NAT2*		*NAT1*				Exposure assessment	Article
	Type	No.	Type	No.	RR* for fast and intermediate acetylators vs. slow acetylators	95% CI*	Alleles investigated	Genotype comparison	RR	95% CI		
Japan	Cases of histologically confirmed colorectal cancer; 53% male	234	"Healthy" volunteers	329	0.8	0.5, 1.4					None	Shibuta et al., 1994 (40)
Japan	Colon tissue samples from colorectal cancer cases obtained at surgery in three hospitals in Kanazawa; mean age = 67.2 years (range, 38–81); 44% male	36	Liver autopsy samples age-matched to cases	36	1.0	0.2, 4.7					None	Oda et al., 1994 (122)
Portugal, Lisbon	Unrelated colorectal cancer patients from Lisbon area; mean age = 64.2 years (SD* 11), 63% male	114	Recruited from medical check-ups; mean age of 46 years (SD 19.6)	201	2.0	1.3, 3.2					None	Gil et al., 1988 (66)
Singapore	Chinese colorectal cancer patients recruited from surgical departments of two hospitals; mean age = 47 years; 59% male	216†	"Healthy" undergraduates and blood donors; mean age = 27 years; 73% male	187	1.1	0.7, 1.7	*NAT1*3* *NAT1*4* *NAT1*10* *NAT1*11*	Not stated	1.0‡		None	Lee et al., 1998 (125)
United Kingdom, Lothian	Consecutive series of operable patients with colorectal cancer from four hospitals	275	"Healthy" individuals attending occupational screening clinics	343	0.8	0.6, 1.2					None	Hubbard et al., 1997 (78)
United Kingdom, Newcastle and North Tyneside	Population-based cases of colorectal cancer; source not stated; median age of 69 years, 59% male	174	Population-based controls selected from primary care registers, matched with cases on age, sex, and general practitioner	174	1.0	0.6, 1.5					Diet assessed by food frequency questionnaire; smoking status and alcohol intake assessed; exposure analyzed with genotype	Welfare et al., 1997 (81)
United Kingdom, North Staffordshire	Sample of incident cases of colorectal adenocarcinoma from one hospital	202	Hospitalized patients undergoing treatment for noncancerous conditions	112	1.1	0.7, 1.8	*NAT1*3* *NAT1*4* *NAT1*10* *NAT1*11*	Heterozygous/homozygous *NAT1*10* vs. all others	1.9	1.2, 3.1	Smoking status available for cases only; analyzed with genotype	Bell et al., 1995 (25)
United Kingdom, Scotland	Consecutive series of operable patients with colorectal cancer from three hospitals	260	"Healthy" individuals attending occupational screening clinics	323			*NAT1*4* *NAT1*14* *NAT1*15*	*NAT1*4/*15* or *NAT1*4/*14* genotypes vs. *NAT1*4/*4* genotype	1.0‡		None	Hubbard et al., 1998 (95)

United States	Colorectal cancer samples obtained from Disease Research Interchange and Co-operative Human Tissue Network; mean age = 62 years; 61% male, 72% White	44	Noncancer colon samples from same sources as cases; mean age = 53 years; 21% male; 75% White	28	1.0	0.4, 2.5					None	Rodriguez et al., 1993 (8)
United States, Los Angeles County, California	Subjects who had undergone sigmoidoscopy, where a colorectal adenoma was found; 64% male; 55% White, 16% Black, 17% Hispanic, 10% Asian	447§	Subjects who had undergone sigmoidoscopy and had no current or past polyp; similar age, sex, and ethnic distribution as cases	487§	1.1	0.8, 1.4	*NAT1*10*	Heterozygous/homozygous *NAT1*10* vs. all others			Smoking status assessed and analyzed with genotype	Probst-Hensch et al., 1995 (124) and 1996 (30)
United States, Los Angeles and Orange County, California	Subjects who had undergone sigmoidoscopy, where a colorectal adenoma was found; ages 50–74 years	528	Subjects who had undergone sigmoidoscopy and had no current or past polyps, individually matched to cases	565	—#		*NAT1*11* *NAT1*14* *NAT1*15* *NAT1*17* *NAT1*19* *NAT1*20* *NAT1*21* *NAT1*22* *NAT1*23* *NAT1*25*	Low activity *NAT1* mutation (**14*, **15*, **17*, **19*, or **22*) vs. all other alleles combined	0.8	0.4, 1.5	Smoking, exercise, diet, and family history assessed by questionnaire; not analyzed with genotype	Lin et al., 1998 (24)**
United States, Minnesota	Individuals undergoing colonoscopy at private gastroenterology practices and found to have:		Individuals undergoing colonoscopy at private gastroenterology practices and found to be polyp-free	633							Smoking status, pack-years of smoking; analyzed with genotype	Potter et al., 1999 (31)
	at least one adenoma	527			1.1††	0.9, 1.4						
	at least one hyperplastic polyp and no adenomas	200			1.1	0.8, 1.6						
United States, Utah‡‡	Population-based cases of colorectal cancer; source not stated	1,306§§	Population-based controls; source not stated	1,533§§	1.0¶¶		Not stated	Not stated	1.2	0.8, 1.8	None	Jenkins et al., 1997 (123)
United States, Utah	Cases of primary colon cancer only; persons with rectal cancer, known familial adenomatous polyposis, ulcerative colitis, or Crohn's disease were excluded	1,611	Controls randomly selected to meet the age and sex distribution of cases from medical care program lists, driver's license lists, Social Security lists, and random digit dialing	1,955	1.1##	0.9, 1.2					Various measures of smoking and meat consumption assessed***; analyzed with genotype	Slattery et al., 1998 (37); Kampmann et al., 1999 (126)
United States, multicenter	Male cases with colorectal cancer in the Physicians' Health Study cohort, ascertained from questionnaires, with confirmation from medical records and the National Death Index	212	Controls selected from the same cohort who had not developed cancer at the time the case was diagnosed	221	0.8	0.5, 1.3	*NAT1*3* *NAT1*4* *NAT1*10* *NAT1*11*	Heterozygous/homozygous *NAT1*10* vs. all others	0.9	0.6, 1.5	Meat intake assessed by food frequency questionnaire; analyzed with genotype	Chen et al., 1998 (38)

Table continues

TABLE 4. Continued

* RR, relative risk; CI, confidence interval; SD, standard deviation.
† 68 cases were included in the analysis of *NAT1*.
‡ The authors stated that no significant differences in the frequencies of *NAT1* alleles between cases and controls were observed.
§ 441 cases and 484 controls were included in the analysis of *NAT1*.
¶ Negative sigmoidoscopy within previous 5 years.
# No relative risk reported. The authors stated that there was no increased frequency of adenomas among subjects with the *NAT2* fast acetylator genotype.
** This study included the subjects investigated by Probst-Hensch et al. (30, 124).
†† Crude relative risks. The authors presented relative risks for 1) adenomas, fast vs. slow: RR = 1.1 (95% CI: 0.6, 1.9); 2) adenomas, intermediate vs. slow: RR = 1.1 (95% CI: 0.8, 1.4); 3) hyperplastic polyps, fast vs. slow: RR = 0.9 (95% CI: 0.4, 1.9); and 4) hyperplastic polyps, intermediate vs. slow: RR = 1.2 (95% CI: 0.8, 1.6), adjusted for age, sex, nonsteroidal antiinflammatory drug use, hormone therapy use, and smoking.
‡‡ Abstract only.
§§ 146 cases and 183 controls were included in the analysis of *NAT1*.
¶¶ 95% confidence interval could not be computed.
Crude relative risk. Slattery et al. (37) presented relative risks for men and women separately, adjusted for age, energy intake, body mass index, long term physical activity, dietary fiber, and usual number of cigarettes smoked per day. Men: RR = 0.9 (95% CI: 0.6, 1.2); women: RR = 1.0 (95% CI: 0.7, 1.6).
*** Slattery et al. (37) included data on smoking; Kampmann et al. (126) included data on meat consumption.

significant positive association with fast acetylation genotypes (RR = 2.0; 95 percent CI: 1.3, 3.2) (66).

Several issues affect the interpretation of these studies. Two studies were based on tissue samples, obtained either at surgery (122) or from a tissue sample bank (8). No association was apparent in either study. However, there was little information on the subjects from whom the samples were obtained, and the number of samples was small (<50), which limited statistical power. The other studies were all based on at least 100 cases. However, the study in which a significant association was found was the smallest of these (66). In this study, controls were statistically significantly younger than cases; if *NAT2* genotype were associated with survival, this may have biased the relative risk. In addition, the areas of residence of the cases and controls differed (66).

Three studies included controls who would be expected to have been representative of the population at risk of developing the disease (37, 38, 81). In the other studies, either the controls may not have been representative of the population at risk (8, 25, 66, 78, 122, 125) or the methods of control selection were not clearly described (40, 123).

The methods of case selection varied between studies, which may have affected their comparability. For example, Hubbard et al. (78) included operable cases, and Bell et al. (25) included a "sample" of incident tumors. If the reasons for exclusion were related to disease etiology or progression, this might have influenced the observed result. The study by Slattery et al. (37) related only to colon cancer, whereas the others also included rectal cancer (but would have had lower statistical power to investigate subsite-specific associations).

Although only one study (66) observed an association between colorectal cancer and *NAT2* genotype, other studies have detected associations within subgroups. Hubbard et al. (78) reported a positive association between colorectal cancer and slow acetylation among subjects under 70 years of age (RR = 1.7; 95 percent CI: 1.1, 2.6). In contrast, Slattery et al. (37) reported a positive association between colon cancer and fast/intermediate acetylator status among older women (aged ≥67 years) (RR = 1.4; 95 percent CI: 1.0, 1.8). In one study, data on specific *NAT2* alleles were presented (125). There was a positive association between the *NAT2**7A allele and colorectal cancer (RR = 2.4; 95 percent CI: 1.5, 3.9). However, the interpretation of this finding is limited by the potential selection bias noted above.

Colorectal cancer and *NAT1* genotype

Investigations of NAT1 and colorectal cancer were prompted by observations that NAT1 is expressed to a greater extent than NAT2 in the colon. It would therefore be expected that localized activation of heterocyclic or aromatic amines within the colon would be predominantly due to NAT1 (8, 9). The low frequency of some *NAT1* allelic variants could result in limited statistical power to detect any effect.

An association between *NAT1* and colorectal cancer was observed in only one (25) of five studies (table 4). That study investigated a limited selection of the most common alleles and found a statistically significant increased risk associated with *NAT1**10 (RR = 1.9; 95 percent CI: 1.2, 3.1). These investigators had previously demonstrated that *NAT1**10 was associated with higher acetylation activity in colon tissue (127). In the studies by Chen et al. (38) and Lee et al. (125), genotypes were assigned on the basis of the alleles investigated by Bell et al. (25). Jenkins et al. (123) did not specify the alleles investigated, and Hubbard et al. (95) only investigated two relatively uncommon alleles.

Colorectal cancer and combined *NAT1* and *NAT2* genotypes

Five studies that determined *NAT1* and *NAT2* genotypes also investigated the effect of combinations of these genotypes (25, 38, 95, 123, 125). None reported any increased risk associated with any combination of *NAT1*/*NAT2* genotypes. However, the statistical power to investigate some of these combinations would have been low. In addition, the limitations regarding study design and alleles detected discussed above also apply.

Colorectal polyps and acetylator genotype

Three studies have investigated the relation between colorectal polyps and aspects of NAT genotype (24, 30, 31, 124) (table 4). No association was found between *NAT1* or *NAT2* genotype and adenomas. However, an association between *NAT1**10 and risk was found when the cases were restricted to "incident" adenomas (i.e., those with negative sigmoidoscopy results within the previous 5 years) (30). Subjects were recruited from persons undergoing sigmoidoscopy. It is possible that some of the controls may have harbored adenomatous polyps out of reach of the sigmoidoscope; this would have biased any association with NAT genotypes toward the null. Probst-Hensch et al. (30) suggested that the lack of an overall association might reflect the presence of undetected *NAT1* mutations. However, the results of subsequent reanalysis (24) in which the *NAT1* gene was screened for mutations but no association between genotype and disease was found make this unlikely. One study analyzed separately individuals with hyperplastic polyps only (31). No association was found between *NAT2* genotype and disease.

Inconsistency between phenotype and genotype studies

Overall, the studies involving assessment of genotype provide little evidence of an association between acetylator status and risk of colorectal lesions. However, the studies of phenotype suggest a positive association between fast acetylation and disease risk. This inconsistency could be due to discordance between genotype and phenotype. As suggested above, the designation of the *NAT2* and *NAT1* genotypes to imputed phenotype is not yet definitive. Discrepancies between genotype and phenotype have been observed in approximately 5–7 percent of subjects assessed in studies of European populations (128). However, fast acetylation status per se would not be expected to raise risk in the absence of exposure to NAT substrates; therefore, it is likely that the genotyping studies more accurately reflect risk attributable to acetylation status alone. The explanation for the increased risk observed in the phenotype studies is not clear, but possible contributing factors include alteration of acetylation phenotype by the presence of disease, selection or participation bias of cases and/or controls, confounding of phenotype by exposures which cause colorectal cancer, and chance.

INTERACTIONS

It would not necessarily be expected that NAT genotype would be independently associated with risk of colorectal neoplasia. If the NAT genes have a role in the etiology of colorectal neoplasia, it is likely that it is a role as a modifier of the relations between particular environmental exposures and disease. Mechanisms by which environmental exposures might lead to malignancy, involving NATs, other enzymes, and concomitant exposure to their substrates, have been proposed (129).

The NAT substrates are also substrates for other enzymes in the putative detoxification/activation pathways of aromatic amines (129). A substrate may be either hydroxylated or *N*-acetylated by cytochrome P450 or NAT, respectively. The hydroxylated substrate may undergo *O*-acetylation catalyzed by NAT. The metabolic fate of each substrate depends on the relative activity, specificity, and affinity of the enzymes in these competing pathways toward that substrate. It is not clear at present how the metabolic fate of specific substrates may be affected by the various allelic forms of the NAT genes.

Of the 11 studies of colorectal cancer and *NAT2* genotypes, only three assessed possible exposure of both cases and controls to NAT substrates and analyzed this together with genotype (37, 38, 81); one other study provided genotype-exposure data for cases only (25). The three studies investigating colorectal adenomas all collected exposure data (24, 30, 124); however, only one analyzed this with genotype (124). Most of the studies which have investigated interactions have had relatively small numbers of subjects in the acetylator status-environmental exposure subgroups, which limited statistical power to detect an interaction should one have been present.

NAT genotype and dietary exposures

The joint effects of dietary exposure and NAT genotype were investigated in three studies (38, 81, 126). Among *NAT2* fast acetylators, Welfare et al. (81) found a significantly raised risk of colorectal cancer associated with consumption of fried meat more than twice weekly as compared with less frequent consumption (RR = 6.0; 95 percent CI: 1.3, 55.0). This was not found among slow acetylators. In the study by Chen et al. (38), among fast acetylators (based on combined *NAT1**10 and fast/intermediate *NAT2* genotypes) the relative risks for >0.5–1 and >1 daily servings of red meat versus ≤0.5 daily servings were modestly but nonsignificantly raised (>0.5–1 daily servings: RR = 2.1 (95 percent CI: 0.81, 5.65); >1 daily servings: RR = 2.4 (95 percent CI: 0.77, 7.12)). This was not seen in non-fast acetylators. This pattern was more pronounced among subjects aged ≥60 years. However, the test for interaction was not statistically significant either for subjects of all ages ($p = 0.16$) or for older subjects ($p = 0.25$). The method by which the red meat was cooked was not reported, nor was preference for well-done meat.

Kampman et al. (126), in further analysis of the subjects included in the study by Slattery et al. (37), investigated associations between various measures of meat consumption, *NAT2* genotype, and colon cancer. Among persons with the intermediate/rapid genotype, there were modestly raised risks associated with 1) higher consumption of red meat, 2) a preference for well-done red meat, 3) high levels of a red meat mutagen index, 4) higher consumption of processed meat, and 5) higher levels of a total meat mutagen index. Unexpectedly, consumption of white meat was more strongly associated with risk among slow acetylators, but the relative risks were only modestly raised.

NAT phenotype and dietary exposures

Two studies have investigated interactions between acetylator phenotype and diet and risk of colorectal lesions, with inconsistent results (118, 120). Wohlleb et al. (118) modeled various aspects of diet, phenotype, and colorectal cancer risk. While consumption of luncheon meat and pork were each significantly associated with disease risk, the introduction of acetylator status into the model had no significant effect.

Roberts-Thomson et al. (120) stratified subjects into slow and fast acetylator phenotype groups and assessed the linear trend in risk of 1) adenoma and 2) cancer across three categories of meat intake (low, medium, and high) in the two strata. It is not clear how these categories of meat intake were determined. Among slow acetylators, there was no association between meat intake and risk of adenoma. Among fast acetylators, adenoma risk increased with increasing meat consumption (continuous variable: RR = 2.1 (95 percent CI: 0.9, 4.7); p for linear trend = 0.08). For colorectal cancer, among slow acetylators the relative risk did not differ significantly from 1 across the categories of meat intake. Among fast acetylators, cancer risk increased with meat intake (continuous variable: RR = 1.7 (95 percent CI: 0.9, 3.5); p for linear trend = 0.13).

NAT genotype and smoking

The possibility of an interaction between NAT genotype and smoking was assessed in four studies (31, 37, 81, 124), with inconsistent results. Slattery et al. (37) found a modest association between several measures of tobacco exposure and colon cancer in men and women, but this effect was modified only slightly by *NAT2* genotype.

In their study of hyperplastic polyps and adenomas, Potter et al. (31) also found significant associations between smoking status and pack-years of smoking and both types of polyps, but these associations were not modified by *NAT2* genotype. Welfare et al. (81) reported that cigarette smoking in the past 5 years was not associated with cancer risk among *NAT2* fast acetylators, but it was associated with significantly raised risk among slow acetylators (RR = 2.3; 95 percent CI: 1.2, 4.6).

In their study of adenomas, Probst-Hensch et al. (124) observed a raised risk in current smokers who were *NAT2* fast acetylators in comparison with persons who had never smoked and were slow acetylators (RR = 2.3; 95 percent CI: 1.0, 5.2). Consistent with this, in an analysis of colorectal cancer cases only, *NAT1**10 was found to occur more frequently among smokers (52 percent) than among nonsmokers (41 percent) (25). *NAT2* fast acetylator genotypes were also more common among smokers (52 percent) than among nonsmokers (45 percent).

NAT genotype and other genes

Other enzymes in the detoxification/activation pathway are also polymorphic. For example, the glutathione *S*-transferase class M1 (*GSTM1*) and glutathione *S*-transferase class T1 (*GSTT1*) genes, involved in detoxification, are polymorphic (130); functionally significant alleles of cytochrome P4501A1 (*CYP1A1*) have been reported (131); and genetic polymorphism in cytochrome P4501A2 (*CYP1A2*) has recently been demonstrated (132, 133). This raises the possibility that these genes may interact to affect disease risk. Gene-gene-environment interactions have been investigated in three studies (37, 121, 124).

Slattery et al. (37) stratified their subjects by joint *GSTM1* and *NAT2* genotype and investigated colon cancer risk associated with smoking within each stratum. Among men who were *NAT2*-slow and *GSTM1*-null, the relative risks associated with smoking <20 and ≥20 cigarettes per day, compared with not smoking, were 1.4 (95 percent CI: 0.8, 2.3) and 1.7 (95 percent CI: 1.2, 2.6), respectively. This trend was not observed in other genotype strata or among women. Probst-Hensch et al. (124) reported a significantly raised risk of adenomas for fast acetylators who were *GSTM1*-null in comparison with slow acetylators who were *GSTM1*-non-null among current smokers (RR = 10.3; 95 percent CI: 1.94, 55.0). This genotype combination was not associated with raised risk among never smokers (RR = 1.0; 95 percent CI: 0.5, 2.2).

Lang et al. (121) considered the joint effects of NAT2 phenotype, CYP1A2 phenotype (rapid or slow) and meat cooking preference (rare/medium or well-done) on risk of colorectal cancer and polyps combined. The reference category comprised subjects who were NAT2-slow and CYP1A2-slow and preferred rare/medium meat. The relative risk for subjects who were NAT2-rapid/CYP1A2-rapid and preferred rare/medium meat was 3.1, and the relative risk for subjects who were NAT2-rapid/CYP1A2-rapid and preferred well-done meat was 6.5. Confidence intervals were not reported. The result of the test for interaction was not significant. It is likely that each stratum contained few subjects.

LABORATORY TESTS

Early case-control studies on acetylation and colorectal cancer used phenotyping methodologies (table 3). The NAT genotyping techniques currently used in epidemiologic studies rely on initial amplification of the region of the gene in which the polymorphisms are found. Following amplification, restriction fragment length polymorphism analysis and allele-specific polymerase chain reaction are most commonly used. An oligo-ligation assay has recently been developed, and it is particularly suitable for automated studies (134).

Because of the marked interethnic differences in NAT genotypes, it is important that the appropriate mutations be investigated so that alleles can be assigned correctly. Failure to fully define alleles may bias the estimate of imputed acetylator phenotype. For example, Lin et al. (24) reanalyzed samples from the study by Probst-Hensch et al. (124) and recategorized 20 subjects who had been classified as fast acetylators in the original study as slow acetylators. In addition, if additional substitutions are not explicitly detected by the techniques employed but are assumed to be present due to previously observed linkage patterns, it is important that this be explicitly stated in the characterization of the alleles.

POPULATION TESTING

There is currently insufficient evidence implicating polymorphic NAT genes in the etiology of colorectal cancer or adenomatous polyps to justify population testing.

INTERNET SITES

Internet sites pertaining to colorectal cancer and genetic mutations are listed in the Appendix table.

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APPENDIX TABLE. Internet sites pertaining to colorectal cancer and genetic mutations

Type of site	World Wide Web URL
Data on disease frequency	
International Agency for Research on Cancer—Cancer Mondial	http://www-dep.iarc.fr/
Surveillance, Epidemiology, and End Results (SEER) Program	http://www-seer.ims.nci.nih.gov/
Information on cancer	
Cancer Research Campaign	http://www.crc.org.uk/homepage.html
American Association of Cancer Research	http://www.aacr.org/
National Cancer Institute	http://cancernet.nci.nih.gov/
International Union against Cancer	http://www.uicc.ch/
Genetic information	
Office of Genetics and Disease Prevention, Centers for Disease Control and Prevention—Medical Literature Search	http://www.cdc.gov/genetics/Medical.htm
Public Health Genetics Unit	http://www.medinfo.cam.ac.uk/phgu/
Human Gene Mutation Database	http://www.uwcm.ac.uk/uwcm/mg/hgmd0.html
Online Mendelian Inheritance in Man (OMIM)	http://www.ncbi.nlm.nih.gov/Omim/
GenAtlas	http://bisance.citi2.fr/GENATLAS/
UniGene	http://www.ncbi.nlm.nih.gov/Schuler/UniGene/
GeneCards	http://bioinfo.weizmann.ac.il/cards/
National Center for Biotechnology Information	http://www.ncbi.nlm.nih.gov/
Links to chromosome-specific databases and other sites	http://cedar.genetics.soton.ac.uk/public_html/links.html